IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PCT National Stage Application of:	Confirmation No.: 6943
Glue, *et al.*	Art Unit: 1614
U.S. Application No.: 10/576,052	Examiner: Spivack, Phyllis G.
Filing or 35 USC §371 Date: 1 November 2006	Atty. Docket: 33427-US-PCT (62106.00011)
International Application No: PCT/EP2004/012081	
Filed: 26 October 2004	
For: **Use Of Neurokinin Antagonists In The Treatment Of Urinary Incontinence**	

DECLARATION OF ECKHARD WEBER UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Eckhard Weber, do declare that:

1. I am a co-inventor of the inventions disclosed and claimed in US Patent Application Serial No. 10/576,052 (hereinafter referred to as the "Application").

2. I am a PhD scientist and am currently working in the Gastrointestinal Disease Area at Novartis Pharma AG in Horsham, England of the United Kingdom. I have more than 15 years of experience in pre-clinical research, including over two years of pre-clinical research involving urinary incontinence.

3. I have reviewed the office action dated 7 July 2009 in which the Examiner rejected Claims 1-8 under 35 U.S.C. §103(a) as being unpatentable over U.S.

2004/0058914 (hereinafter referred to as the "Doi reference" or "Doi"). I have also carefully reviewed the Doi reference. In the Office Action the Examiner states that Doi teaches the administration of the neurokinin-receptor antagonist DNK333 (the compound of formula II in Claim 7 of the present Application) for the treatment of urinary incontinence.

4. As one skilled in the art of pre-clinical pharmaceutical research, I hereby present evidence in support of non-obviousness of the Claims of the present Application, including secondary considerations such as unexpected properties attributed to DNK333, the compound of formula II in Applicants' Claim 7. I also present my opinion regarding the purported teachings of Doi, specifically related to the purported teaching of the administration of DNK333 for the treatment of urinary incontinence.

5. Upon careful review of the data and Examples presented in the Doi reference, it is my opinion that Doi does not demonstrate that any of the compounds disclosed therein are effective to treat urinary incontinence. The only experimental data in Doi demonstrates the effectiveness of a combination of disclosed compounds in increasing cyclophosphamide-impaired bladder capacity (not urinary incontinence). The model used in Doi's Experimental Examples 1 and 2 that purportedly tested for the efficacy of a composition with respect to urinary incontinence, but which instead tested for the efficacy of a composition with respect to increasing bladder capacity, was based on the treatment of animals under urethane anesthesia. Moreover, these experiments were apparently performed in rats[1], and data generated in rat models are considered to be of low predictability for humans because of the low homology of rat and human NK_1 receptors, (See Beresford et al., "Investigation into species variants in tachykinin NK_1 receptors by use of the non-peptide antagonist, CP-96,345, "British Journal of

[1] It is unclear whether the experiments were performed in rats (as described in the text of Experimental Examples 1 and 2) (see paragraphs [0501] and [0503] of the Doi reference) or in guinea pigs (as described in Tables 1 and 2 in Experimental Examples 1 and 2). Since the text refers multiple times to rats, it is believed that the model used in the Doi reference was a rat model, as opposed to a guinea pig model.

Pharmacology, Vol. 104, No. 2, pp 292-293 (1991). (A copy of this article was previously submitted with my declaration under Section 37 C.F.R. §1.132 dated 17 September 2008.)

6. Urinary incontinence is generally attributed to sphincter incompetence or detrusor muscle overactivity, both of which involve a neuromuscular mechanism. Both sphincter incompetence or detrusor muscle overactivity involve a neuromuscular mechanism for urinary incontinence. Doi, however, does not recognize that urinary incontinence involves a neuromuscular mechanism. In addition, the model used in the Doi reference, is a model that is not directed towards a neuromuscular mechanism for urinary incontinence and is not a model for urinary incontinence. This would be readily apparent to one of ordinary skill in the art and would be taken into consideration when determining whether or not a compound could be useful for treating urinary incontinence. In other words, when considering the lack in Doi of a model for urinary incontinence and the lack of any experimental evidence in Doi that any of the Doi compounds are useful for urinary incontinence, one of ordinary skill in the art would not conclude that all of the compounds of Doi were useful for treating urinary incontinence, much less that DNK333 was useful for treating urinary incontinence.

7. In contrast to the Doi reference, an *in vivo* model of stimulated micturition in conscious guinea pigs and an isolated guinea pig detrusor contractility model were used in the present Application (see Specification, p. 10, paragraph 2). Guinea pig models were used because of the high homology of guinea pig and human NK receptors. The *in vivo* model of stimulated micturition (see Example 1 of the Specification) is based on the subcutaneous administration of 5-hydroxytryptophan (5-HTP), which is a precursor for serotonin, which is a key neurotransmitter of the viscera and triggers neuromuscular detrusor contractions. The other model (see Example 2 of the Specification) is based on the application of substance P, which is the endogenous ligand for NK receptors and also a key neurotransmitter triggering neuromuscular detrusor contractions. Both models used in the present Application tested DNK333, focused on neuromuscular mechanisms for urinary incontinence, such as a

neuromuscular mechanism of detrusor overactivity, and are models for non-inflammatory overactive bladder/urinary incontinence. Therefore, unlike Doi, the experimental results in the present Application demonstrate preclinical efficacy of the compounds for the treatment of urinary incontinence.

8. The Examiner states that Green, et al., "Efficacy and Safety of a Neurokinin-1 Receptor Antagonist in Postmenopausal Women with Overactive Bladder with Urge Urinary Incontinence," The Journal of Urology, Vol. 176, pp. 2535-2540 (2006) describes the administration of the NK_1 receptor antagonist, aprepitant, which is not an NK_1-NK_2 dual antagonist and which is not structurally related to DNK333. As a result, the Examiner concludes that "the comparison is misplaced and without merit." (See Office Action, page 3.)

9. The Green article was cited as evidence that the model used in the Experimental Examples in Doi is not a model for urinary incontinence. If it were a model for urinary incontinence, then it should not have produced data inconsistent with the clinical data of the Green article (i.e., it should not have generated data showing that NK_1 receptor antagonists alone are not effective in treating urinary incontinence whereas the Green article demonstrates that NK_1 receptor antagonists can be effective alone in treating urinary incontinence). Even though the compound in the Green article is not structurally similar to DNK333 and is apparently not an NK_1-NK_2 dual antagonist, the Green article is relevant because it provides experimental evidence that the model used in the experimental examples of Doi that purport to show efficacy for urinary incontinence is not in fact a model for urinary incontinence and that Doi therefore provides no experimental evidence that any of its compounds are effective in the treatment of urinary incontinence.

10. In paragraphs [0505] and [0506], Doi claims that the combined use of an NK_1 receptor antagonist and an anti-cholinergic drug or NK_2 receptor antagonist is effective in treating 14 diseases and conditions, namely urinary frequency, urinary incontinence, asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, osteoarthritis,

pain, cough, irritable bowel syndrome, emesis, depression, anxiety, manic depression psychosis and schizophrenia.

11. Doi focuses on combination therapy of NK_1 receptor antagonists and in particular on the administration of (i) an NK_1 antagonist and (ii) an NK_2 antagonist and/or an anti-cholinergic drug. (See the Abstract of Doi. See also Examples 1 – 4 on page 28 of Doi where the administration of at least two compounds is taught and Experimental Examples 1 and 2 on pages 28 and 29 where two compounds are administered.) Doi states that compound (T) is an NK_1 receptor antagonist and is "particularly preferable." (See paragraph [0063] in Doi.) In paragraphs [0275] through [0384], Doi identifies 110 preferred compounds, none of which is DNK333. Doi essentially mentions in passing that an NK_1-NK_2 dual antagonist can be administered alone, but does not provide any experimental examples of the administration of an NK_1-NK_2 dual antagonist alone.

12. In order to provide further facts and arguments in support of non-obviousness of Applicants' Claims, additional data is hereby presented and attached as Exhibit A hereto, which show unexpected properties attributed to Applicants' claimed inventions. These data show that the compound of formula II (i.e., DNK333) exhibits unexpected properties compared to the multitude of compounds known in the art for the treatment of urinary incontinence. Firstly, DNK333 does not only act on NK_1 and NK_2 receptors, but is a triple antagonist acting on NK_1, NK_2 and NK_3 receptors. (See Examples 1 and 2 of Exhibit A). Secondly, as demonstrated by clinical studies, DNK333 administration is associated with unusually few side effects, i.e., shows excellent clinical safety and tolerability. (See Example 3 of Exhibit A).

13. Regarding Exhibit A, Example 1 shows that DNK333 binds to all three human recombinant neurokinin receptors, namely NK_1, NK_2 and NK_3. Example 2 describes results from functional assays using DNK333 with and without competitive agonists of human native NK_1, NK_2 and NK_3 receptors. As can be seen in Figure 1, increasing amounts of DNK333 were able to competitively block all three receptor subtypes in a concentration-dependent fashion. This further corroborates the findings shown in

Example 1 that DNK333 binds all three receptor subtypes (i.e., is a triple antagonist) and is able to effectively compete with the respective receptor agonist.

14. Example 3 describes a clinical study performed with DNK333 and summarizes its results in Table 2. These data show that DNK333 is characterized by a surprisingly high clinical safety and tolerability in patients.

15. Importantly, these data indicate that DNK333 is not only a compound that can be used in the laboratory, but rather can be used as a medicament in a clinical setting to treat patients suffering from urinary incontinence.

16. In order to appreciate the significance of these results, it needs to be understood that urinary incontinence is based on a unique pathophysiological role of several neurokinin receptors. One of ordinary skill in the art would readily appreciate the various neurokinin-receptor subtypes and appreciate their role in urinary incontinence. For example, all three neurokinin receptors, NK_1, NK_2 and NK_3, are expressed on cells modulating urinary bladder motor and sensory function. They are solely involved in exaggerated conditions such as those found in urinary incontinence. In other words, it has been found that DNK333 can block multiple neurokinin receptors that are involved in urinary incontinence.

17. Thus, one of ordinary skill in the art would expect that DNK333 as a triple antagonist would provide for an improved treatment of urinary incontinence compared to a monofunctional NK_1 or NK_2 antagonist, or even a dual antagonist, specifically because urinary incontinence is a disease that involves all three receptors NK_1, NK_2 and NK_3. Moreover, low toxicity and high tolerability of DNK333 further account for an advantageous use.

18. The blockade of multiple neurokinin receptors with a single compound to treat urinary incontinence constitutes an innovative approach to interfere with

pathophysiological mechanisms of urinary incontinence in a polymodal fashion without impairment of normal functions.

19. This unexpected property is lacking in Doi; in Doi there is no indication that DNK333 would bind to all three receptor subtypes or that DNK333 would have any other advantageous properties compared to the other compounds disclosed therein.

20. According to the Examiner, motivation is provided based on the teachings and suggestions of Doi to administer DNK333 to treat urinary incontinence. (See Office Action, page 3.) Doi, however, fails to provide any motivation for one of ordinary skill in the art to specifically select DNK333 from all the various compounds disclosed in Doi and fails to provide any reasonable expectation of success for treating urinary incontinence if DNK333 were selected, especially since the sole experimental model utilized in Doi is not a model for urinary incontinence and all of the examples in Doi are directed to combination therapy. Thus, one of ordinary skill in the art would not have arrived at an improved method of treating urinary incontinence using DNK333 which has superior properties without exerting inventiveness. In view of the focus of Doi on combination therapy, Doi teaches away from Applicants' claimed inventions and would lead one of ordinary skill in the art down an entirely different path when investigating a method of treating urinary incontinence.

21. In view of the lack of experimental evidence that any of the compounds of Doi are useful in the treatment of urinary incontinence, the unsubstantiated claim in paragraphs [0505] and [0506] of Doi that the combined use of an NK_1 receptor antagonist and an anti-cholinergic drug or NK_2 receptor antagonist is effective in treating 14 diseases and conditions ranging form cough to urinary incontinence to schizophrenia, the numerous compounds disclosed in Doi, the focus on combination therapy in Doi, the lack of any experiments in Doi where a single compound as opposed to a combination of compounds is used, the lack of recognition in Doi of the unexpected properties of DNK333 as a triple neurokinin receptor antagonist and its low toxicity and high tolerability in humans, one of ordinary skill in the art, despite the disclosure in Doi

of DNK333 and the statement in Doi that NK_1-NK_2 dual antagonists may be used alone, would not be motivated to select DNK333 from the numerous compounds disclosed in Doi for the treatment of urinary incontinence nor have any reasonable expectation that a single compound selected from the numerous compounds disclosed in Doi would be successful in treating urinary incontinence. There would be no reasonable expectation of success with respect to a particular compound disclosed in Doi being able to treat urinary incontinence, much less any reasonable expectation that if DNK333 were selected, it would be effective in treating urinary incontinence.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 7th Jan 2010

Eckhard Weber

Blockade of multiple neurokinin receptors:

A novel mechanism of action for the treatment of urinary incontinence

Example 1: DNK333 – Binding at human recombinant NK1, NK2, and NK3 receptors

DNK 333 is a novel neurokinin receptor antagonist acting at all three receptor subtypes, NK_1, NK_2 and NK_3.

The binding affinity of DNK 333 to human recombinant (hr) NK_1, NK_2 and NK_3 receptors was assessed in transfected CHO cells. The displacement pattern to ^{3}H-[Sar^{9}Met(O$_2$)^{11}]SP for NK_1, ^{125}I-Neurokinin A for NK_2 and ^{125}I-MePhe^7 Neurokinin B for NK_3 revealed DNK 333 to be equipotent at $hrNK_1$ and $hrNK_2$ receptors with high affinity pK_i values of 8.4 and 8.0, respectively and additional relevant affinity at $hrNK_3$ receptors with a pK_i value of 6.9 (Table 1).

Table 1 Affinities of DNK 333 and reference agonists (NK_1: [Sar^{9}Met(O$_2$)^{11}]SP; NK_2: Neurokinin A; NK_3: MePhe^7 Neurokinin B) to human recombinant (hr) NK_1, NK_2 and NK_3 receptors in radioligand binding assays.

	$hrNK_1$ (pK_i)	n	$hrNK_2$ (pK_i)	n	$hrNK_3$ (pK_i)	n
Agonist	*9.21 ± 0.10*	*4*	*9.30 ± 0.09*	*4*	*7.58 ± 0.02*	*3*
DNK 333	*8.43 ± 0.13*	*4*	*8.03 ± 0.22*	*4*	*6.87 ± 0.05*	*3*

Mean ± SEM (n = number of experiments, each performed in duplicate).

Example 2: DNK333 – Functional activity at human native NK1, NK2, and NK3 receptors

In human colon epithelium, the NK_1R, NK_2R and NK_3R agonists, [Sar^9, Met(O$_2$)^{11}]SP, [βAla^8]NKA (4-10) and senktide (1 μM), induced increases in electrolyte secretion amounting to 21.2%, 8.8% and, respectively 3.6% of the maximum responses triggered by the muscarin receptor agonist, carbachol (10 μM). DNK 333 antagonized NK_1R –, NK_2R – and NK_3R –stimulated responses in a concentration – dependent fashion with apparent pIC_{50} values of 8.7, 7.0 and 7.7, respectively (Figure 1).

DNK 333 potently and competitively antagonizes neurokinin-stimulated effects in human tissue preparations by acting at all three neurokinin receptors subtypes, NK_1, NK_2 and NK_3, without attenuating normal functions.

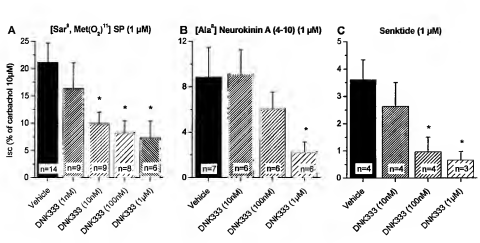

Figure 1: Inhibitory effects of DNK 333 on NK1 R – (A), NK2 R – (B) and NK3 R – stimulated (C) secretion (Isc) in epithelial preparations of human colon. Data are shown as mean ± SEM (significantly different from controls ($p < 0.05$); ANOVA post-hoc Dunnett's test; n = number of patients).*

Example 3: DNK333 – Innovative clinical safety and tolerability profile

The clinical safety and tolerability profile of DNK333 is excellent and similar to placebo.

Clinical safety and tolerability of DNK333 was assessed following ascending single oral doses from 5 to 200 mg in a microemulsion drink solution. Each dose was administered to 9 fasted healthy male subjects, with 6 subjects receiving active drug and 3 receiving placebo. DNK333 and placebo were well tolerated at all six dose levels (5, 10, 25, 50, 100, and 200 mg) and there were no clinically significant changes in physical examination, vital signs (*i.e.* heart rate and blood pressure), ECG recordings, thyroid function tests or clinical laboratory safety data. All subjects completed the study and there were no serious adverse events reported during the study. The most commonly reported adverse event was headache, 4 in the placebo group, 1 episode in each of the 10, 25 and 50 mg groups and 2 in the 200 mg group. They were all of mild severity and all resolved spontaneously with no further action required. There were 5 episodes of

mild postural dizziness, 1 in the placebo group, 2 in the 50 mg group and 1 in each of the 100 and 200 mg groups all resolved spontaneously.

Clinical safety and tolerability of DNK333 was assessed following oral multiple doses of 100 mg bid in a microemulsion drink solution for 7 days. Fifteen healthy male subjects were dosed and completed the multiple dose study as planned. There were no serious adverse events reported during the study. There were no clinically significant changes in vital signs (*i.e.* pulse and blood pressure), ECG recordings, thyroid function tests or laboratory safety data. The most common adverse event reported during the study was headache with 6 subjects reporting 8 events, these were all of mild severity, 7 were suspected to be drug-related. All adverse events resolved spontaneously. Dizziness was the second most commonly reported adverse event with 4 events reported by 4 subjects. Three of these events were reported as postural dizziness of mild severity and all resolved spontaneously. One of the three episodes of postural dizziness was associated with a fall in blood pressure not considered to be clinically significant by the investigator.

Clinical safety and tolerability of DNK333 was assessed in 187 female patients with irritable bowel syndrome following oral multiple doses of 25 mg bid and 100 mg bid as capsule for 2 and 4 weeks. There were no serious adverse events reported during the study. There were no clinically significant changes in vital signs or laboratory safety data. The most common adverse event was headache. Drug-related adverse events were reported to a similar extend in DNK333 treatment groups and placebo groups. They were all of mild severity and all resolved spontaneously with no further action required (Table 2).

Table 2 Most common adverse events in female patients with irritable bowel syndrome during 2-week treatment with DNK333 (25mg and 100 mg bid, trial 1) and 4-week treatment with DNK333 (25mg bid, trial 2).

	Trial 1			Trial 2	
	DNK333 25 mg bid	DNK333 100 mg bid	Placebo bid	DNK333 25 mg bid	Placebo bid
N (%)	(n=42)	(n=43)	(n=50)	(n=102)	(n=77)
Patients with adverse events	18 (42.9)	15 (34.9)	18 (36.0)	38 (37.3)	32 (41.6)
Headache	5 (11.9)	2 (4.7)	3 (6.0)	5 (4.9)	4 (5.2)
Nausea	1 (2.4)	2 (4.7)	2 (4.0)	5 (4.9)	2 (2.6)
Dizziness	2 (4.8)	1 (2.3)	0 (0)	4 (3.9)	3 (3.9)
Abdominal pain	0 (0)	1 (2.3)	2 (4.0)	2 (2.0)	2 (2.6)
Fatigue	2 (4.8)	2 (4.7)	0 (0)	2 (2.0)	2 (2.6)
Back pain	0 (0)	1 (2.3)	2 (4.0)	2 (2.0)	2 (2.6)
Flatulence	0 (0)	2 (4.7)	2 (4.0)	3 (2.9)	0 (0)
Constipation	0 (0)	1 (2.3)	2 (4.0)	2 (2.0)	0 (0)
Muscle spasms	0 (0)	0 (0)	3 (6.0)	1 (1.0)	0 (0)
Dysmenorrhoea	0 (0)	0 (0)	2 (4.0)	0 (0)	0 (0)